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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A01K 67/027, C07K 16/00, 16/24,</b> <b>16/28 // C12N 15/85, 15/90</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 98/24893</b> <b>(43) International Publication Date:</b> 11 June 1998 (11.06.98)
<b>(21) International Application Number:</b> PCT/US97/23091 <b>(22) International Filing Date:</b> 3 December 1997 (03.12.97) <b>(30) Priority Data:</b> 08/759,620 3 December 1996 (03.12.96) US <b>(71) Applicant:</b> ABGENIX, INC. [US/US]; 7601 Dumbarton Circle, Fremont, CA 94555 (US). <b>(72) Inventors:</b> JAKOBOVITS, Aya; 2021 Monterey Avenue, Menlo Park, CA 94025 (US). KUCHERLAPATI, Raju; 8 Gracie Lane, Darien, CT 06820 (US). KLAPHOLZ, Sue; 76 Peter Coutts Circle, Stanford, CA 94305 (US). MENDEZ, Michael; P.O. Box 787, El Granada, CA 94018 (US). GREEN, Larry; 70 Crestline Drive #2, San Francisco, CA 94131 (US). <b>(74) Agents:</b> HALEY, James, F., Jr. et al.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US).	<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>  <b>(88) Date of publication of the international search report:</b> 20 August 1998 (20.08.98)	
<b>(54) Title:</b> TRANSGENIC MAMMALS HAVING HUMAN IG LOCI INCLUDING PLURAL V <sub>H</sub> AND V <sub>κ</sub> REGIONS AND ANTIBODIES PRODUCED THEREFROM		
<b>(57) Abstract</b>  The present invention relates to transgenic non-human animals that are engineered to contain human immunoglobulin gene loci. In particular, animals in accordance with the invention possess human Ig loci that include plural variable (V <sub>H</sub> and V <sub>κ</sub> ) gene regions. Advantageously, the inclusion of plural variable region genes enhances the specificity and diversity of human antibodies produced by the animal. Further, the inclusion of such regions enhances and reconstitutes B-cell development to the animals, such that the animals possess abundant mature B-cells secreting extremely high affinity antibodies.		

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# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 97/23091

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 A01K67/027 C07K16/00 C07K16/24 C07K16/28 //C12N15/85, C12N15/90		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6 A01K C07K C12N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. JAKOBOVITS ET AL., : "Production of antigen-specific human antibodies from mice engineered with human heavy and light chain YACs" ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 764, 1995, NEW YORK, NY, US, pages 525-535, XP002067728 see the whole document but specially pages 533-534 <div style="text-align: center; margin-top: 10px;">           ---            -/--         </div>	1-16
<div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center;">12 June 1998</div>		Date of mailing of the international search report  <div style="text-align: center;">25/06/1998</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  <div style="text-align: center;">Mateo Rosell, A.M.</div>

## INTERNATIONAL SEARCH REPORT

Internat. Application No  
PCT/US 97/23091

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 94 25585 A (GENPHARM INT ) 10 November 1994  cited in the application  see page 1, line 19-33  see page 6, line 24 - page 7, line 23  see page 11, line 6 - page 12, line 19  see page 23, line 25 - page 24, line 7  see page 48, line 35 - page 49, line 22;  examples 1-5  see page 185, line 26 - page 190, line 31  see page 198, line 18-30  see page 202, line 16-36</p>	1,2, 6-10,16, 24
A	<p>WO 96 34096 A (CELL GENESYS INC) 31 October 1996  cited in the application  see page 2, line 20-34  see page 13, paragraph 31-33  see page 15, line 14-21; examples 2,3</p>	1,16,17, 19-21, 23,24
A	<p>WO 91 00906 A (GENETICS INST) 24 January 1991  see the whole document</p>	1,11-16
A	<p>L.D. TAYLOR ET AL.: "A transgenic mouse that expresses a diversity of human sequence heavy and light chain immunoglobulins"  NUCLEIC ACIDS RESEARCH,  vol. 20, no. 23, 1992, OXFORD, GB,  pages 6287-6295, XP002041128  cited in the application  see the whole document</p>	1-16, 26-28
A	<p>M. BRUGGEMAN AND N.S. NEUBERGER:  "Strategies for expressing human antibody repertoires in transgenic mice"  IMMUNOLOGY TODAY,  vol. 17, no. 8, 1 August 1996, OXFORD, GB,  pages 391-397, XP002067729  cited in the application  see the whole document</p>	1-28
P,X	<p>M.J. MENDEZ: "Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice"  NATURE GENETICS,  vol. 15, no. 2, 1 February 1997, NEW YORK, NY, US,  pages 146-156, XP002067603  see the whole document</p>	1-15

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## INTERNATIONAL SEARCH REPORT

Intern. Application No.

PCT/US 97/23091

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	A. JAKOBOVITS ET AL., : "Human immunity in mice engineered with megabase human heavy and kappa light chain YACs" THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, vol. 99, no. 1, part 2, 1 January 1997, SAINT LOUIS, MO, US, page S113 XP002067604 see abstract	1-15
P,X	J.R.F. CORVALAN ET AL., : "Generation of fully human high affinity monoclonal antibodies to EGF receptor in mice" THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, vol. 99, no. 1, part 2, 1 January 1997, SAINT LOUIS, MO, US, page s214 XP002067605 see abstract	1,16,18, 20,22,24
P,X	X.D. YANG ET AL., : "Human monoclonal antibodies to human TNF-alpha generated from mice carrying human Ig loci" THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, vol. 99, no. 1, part 2, 1 January 1997, SAINT LOUIS, MO, US, page s15 XP002067606 see abstract	1,16,19, 20,23,24

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat. Application No

PCT/US 97/23091

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9425585 A	10-11-1994	US 5661016 A	26-08-1997
		AU 3907895 A	29-02-1996
		AU 6819494 A	21-11-1994
		CA 2161351 A	10-11-1994
		EP 0754225 A	22-01-1997
		JP 8509612 T	15-10-1996
		US 5625126 A	29-04-1997
		JP 8140528 A	04-06-1996
WO 9634096 A	31-10-1996	AU 2466895 A	18-11-1996
		EP 0823941 A	18-02-1998
WO 9100906 A	24-01-1991	NONE	



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特許協力条約に基づいて公開された国際出願

<p>(51) 国際特許分類6 A01K 67/027</p>	<p>A1</p>	<p>(11) 国際公開番号 WO98/37757</p> <p>(43) 国際公開日 1998年9月3日(03.09.98)</p>
<p>(21) 国際出願番号 PCT/JP98/00860</p> <p>(22) 国際出願日 1998年3月2日(02.03.98)</p> <p>(30) 優先権データ 特願平9/62309 1997年2月28日(28.02.97) JP</p> <p>(71) 出願人 (米国を除くすべての指定国について) 麒麟麦酒株式会社(KIRIN BEER KABUSHIKI KAISHA)[JP/JP] 〒104-8288 東京都中央区新川二丁目10番1号 Tokyo, (JP)</p> <p>(72) 発明者 ; および</p> <p>(75) 発明者 / 出願人 (米国についてのみ) 富塚一磨(TOMIZUKA, Kazuma)[JP/JP] 吉田 均(YOSHIDA, Hitoshi)[JP/JP] 石田 功(ISHIDA, Isao)[JP/JP] 〒236-0004 神奈川県横浜市金沢区福浦1-13-5 麒麟麦酒株式会社 基盤技術研究所内 Kanagawa, (JP) 花岡和則(HANAOKA, Kazunori)[JP/JP] 〒228-8555 神奈川県相模原市北里1-15-1 北里大学 理学部 生物科学科内 Kanagawa, (JP) 押村光雄(OSHIMURA, Mitsuo)[JP/JP] 〒683-8503 鳥取県米子市西町86 鳥取大学 医学部 生命科学科内 Tottori, (JP)</p>	<p>(74) 代理人 弁理士 平木祐輔, 外(HIRAKI, Yusuke et al.) 〒105-0001 東京都港区虎ノ門一丁目17番1号 虎ノ門5森ビル3F Tokyo, (JP)</p> <p>(81) 指定国 AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO特許 (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 欧州特許 (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許 (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>添付公開書類 国際調査報告書</p>	
<p>(54) Title: PLURIPOTENT CELLS HAVING DISRUPTED INTRINSIC GENES</p> <p>(54) 発明の名称 内因性遺伝子が破壊されている分化多能性保持細胞</p> <p>(57) Abstract A process for constructing a chimeric non-human animal characterized by preparing microcells containing one or more foreign chromosomes or fragments thereof, and transferring the one or more foreign chromosomes or fragments thereof into pluripotent cells through fusion with the microcells; chimeric non-human animals which can be constructed by the above process and offspring thereof; tissues and cells originating in the above animals; methods for using the individuals, tissues and cells of the animals; pluripotent cells containing one or more foreign chromosomes or fragments thereof, a process for constructing these cells, and the use of these cells; pluripotent cells in which at least two intrinsic genes have been disrupted; a process for constructing the above cells by homologous recombination; etc.</p>		

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/00860

A. CLASSIFICATION OF SUBJECT MATTER  
Int.Cl<sup>6</sup> A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
Int.Cl<sup>6</sup> A01K67/027

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
JICST File on Science and Technology  
BIOSIS PREVIEWS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	Nature Genetics, 16[2] (1997) p.133-143 Full text	1-40, 42, 43, 45-53
P, Y	Full text	41, 44, 54-76
Y	JP, 05-328878, A (The Institute of Physical and Chemical Research), December 14, 1993 (14. 12. 93), Full text (Family: none)	1-76
Y	JP, 07-067629, A (K.K. Dinado), March 14, 1995 (14. 03. 95), Full text (Family: none)	1-76
Y	EMBO Journal, 2 (1983) p.1963-1968 Full text	1-76
Y	Proc. Natl. Acad. Sci. USA, 74 (1997) p.319-323 Full text	1-76

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search  
May 21, 1998 (21. 05. 98)

Date of mailing of the international search report  
June 2, 1998 (02. 06. 98)

Name and mailing address of the ISA/  
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/00860

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	WO, 89/05308, A1 (GESELLSCHAFT FUR BIOTECHNOLOGISCHE FORSCHUNG MBH), June 15, 1989 (15. 06. 89), Full text Full text & JP, 02-502426, A	41, 44, 54, 55 1-40, 42, 43, 45-53, 56-63

## 国際調査報告

国際出願番号 PCT/J P 98/00860

## A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int. Cl.<sup>8</sup> A01K67/027

## B. 調査を行った分野

調査を行った最小限資料 (国際特許分類 (IPC))

Int. Cl.<sup>8</sup> A01K67/027

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース (データベースの名称、調査に使用した用語)

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BIOSIS PREVIEWS

## C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
P, X	Nature Genetics, 16[2] (1997) p. 133-143 全文	1-40, 42, 43, 45-53
P, Y	全文	41, 44, 54-76
Y	J P, 05-328878, A (理化学研究所) 14. 12月. 1993 (14. 12. 93) 全文 (ファミリーなし)	1-76

☒ C欄の続きにも文献が列挙されている。☐ パテントファミリーに関する別紙を参照。

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国際調査を完了した日

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国際調査報告の発送日

02.06.98

国際調査機関の名称及びあて先

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C (続き) . 関連すると認められる文献		
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
Y	J P, 07-067629, A (株式会社ディナード) 14. 3月. 1995 (14. 03. 95) 全文 (ファミリーなし)	1-76
Y	EMBO Journal, 2 (1983) p.1963-1968 全文	1-76
Y	Proc. Natl. Acad. Sci. USA, 74 (1977) p.319-323 全文	1-76
Y A	WO, 89/05308, A1 (GESELLSCHAFT FUR BIOTECHNOLOGISCHE FORSCHUNG MBH) 15. 6月. 1989 (15. 06. 89) 全文 全文 & J P, 02-502426, A	41, 44, 54, 55 1-40, 42, 43, 45-53, 56-63